

We claim.

1. An inhibitor of catalytically active memapsin 2 which binds to the active site of the memapsin 2 defined by the presence of two catalytic aspartic residues and substrate binding cleft.

5           2. The inhibitor of claim 1 comprising an isostere of the active site of memapsin 2.

3. The inhibitor of claim 2 comprising a molecule having the general form X- L<sub>4</sub>-P<sub>4</sub>- L<sub>3</sub>-P<sub>3</sub>-L<sub>2</sub>-P<sub>2</sub>-L<sub>1</sub>-P<sub>1</sub>'-L<sub>1</sub>'-P<sub>2</sub>'-L<sub>2</sub>'-P<sub>3</sub>'-L<sub>3</sub>'-P<sub>4</sub>'L<sub>4</sub>'-Y, wherein Px represent the substrate specificity position relative to the  
10 cleavage site which is represented by an -L<sub>0</sub>-, and Lx represent the linking regions between each substrate specificity position, Px, and  
wherein L<sub>0</sub> is a non-hydrolyzable bond and P<sub>1</sub>' is -R<sub>1</sub>CR<sub>3</sub>-, wherein R<sub>1</sub> is a group smaller than CH<sub>2</sub>OH (side chain of serine), and at least two other P positions are a hydrophobic group.

15           4. The inhibitor of claim 3 which is OM99-1.

5. The inhibitor of claim 3 which is OM99-2.

6. The inhibitor of claim 3 having the structure of Figure 11.

7. The inhibitor of claim 3 having the structure of Figure 12.

8. The inhibitor of claim 3 having the structure of Figure 13.

20           9. The inhibitor of claim 3 having the structure of Figure 14.

10. The inhibitor of claim 1 having an K<sub>i</sub> of less than or equal to 10<sup>-7</sup>

M.

11. The inhibitor of claim 1 which binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2.

25           12. The inhibitor of claim 11 having a K<sub>i</sub> of less than or equal to 10<sup>-6</sup>

M.

13. The inhibitor of claim 11 having a K<sub>i</sub> of less than or equal to 2 nM.

14. The inhibitor of claim 13 having a K<sub>i</sub> of less than or equal to 1  
30 nM.

15. The inhibitor of claim 11 having a root mean square difference of less than or equal to 0.5 Å for the side chain and backbone atoms for amino acids 18-379 of memapsin 2.
- 5 16. The inhibitor of claim 1 which is permeable to the blood brain barrier.
17. The inhibitor of claim 1 which blocks cleavage by memapsin 2 under physiological conditions.
18. The inhibitor of claim 1 which is a non-amino acid small molecule.
- 10 19. The inhibitor of claim 18 having a molecular weight of less than 800 Daltons.
20. A method of synthesis of a Leu\*Ala dipeptide isostere.
21. A method for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease comprising administering  
15 to the individual an effective amount of an inhibitor of memapsin 2 having an  $K_i$  of less than or equal to  $10^{-7}$  M or which binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2.
22. The method of claim 21 wherein the inhibitor is administered orally.
- 20 23. The method of claim 21 wherein the inhibitor blocks cleavage of APP.